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### REMARKS

All of pending Claims 30 through 50 have been rejected as under 35 USC Section 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Amendments and remarks have been submitted obviating these rejections.

Regarding rejections in view of the art, Claim 49 has been rejected as unpatentable based upon Poduslo et al. U.S. Patent No. 5,670,477, considered alone. Claims 30 through 40, 42 through 45, and 50 have been rejected as unpatentable over the Poduslo reference considered in combination with several other references. The Examiner's rejections are respectfully traversed in view of the following remarks.

Each of the Examiner's rejections from the Office Action dated May 31, 2002 is addressed in detail below.

#### Rejections Under 35 USC § 112

##### A. Rejection of Claims 30, 49, and 50.

Claims 30, 49, and 50 have all been rejected as indefinite based upon the use of the phrase "substantially hydrophilic conjugate."

The Examiner correctly points out that the Applicants' specification indicates at page 5, lines 20 through 22, that the term "substantially hydrophilic" means that the conjugate of the invention does not contain a substantially lipophilic moiety. The specification also goes further at that location to state that examples of lipophilic moieties include fatty acids and glycolipids. It is pointed out that fatty acids and glycolipids have been used in the art to increase the lipophilicity of a molecule in order to increase the ability of the molecule to pass cell membranes.

The use of the term "substantially" in the context of hydrophilic conjugates should be considered definite in view of the guidelines contained in the specification and since one of ordinary skill in the art would know what is meant by "substantially hydrophilic." Clearly, the specification defines what "substantially lipophilic" means by providing examples such as fatty acids and glycolipids and by pointing out that these substantially lipophilic moieties are known in the art. It is respectfully submitted that the specification conveys to the artisan of ordinary

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skill a clear indication of what is meant by "substantially lipophilic" by providing these examples. Accordingly, the objection to the phrase "substantially hydrophilic" should be obviated.

Although the Applicant disagrees with the Examiner's rejection of Claims 30, 49, and 50, for the reasons stated above, new Claims 51 through 56 have been added that obviate the rejection and to expedite prosecution that are directed to additional aspects of the invention as discussed above. No new matter is introduced nor is any matter introduced that has not already been considered. Pending Claim 32 recites that the polymer is characterized by the absence of lipophilic moieties.

**B. Rejection of Claim 33 and Rejection of Claims 49 and 50.**

Claim 33 has been rejected as unclear because of the use of the phrase "... said nonpeptidic polymer and said peptide are conjugated from solution" to describe covalent attachment of peptide to nonpeptidic polymer. Claims 49 and 50 have been rejected because of the use of the phrase "... peptide covalently linked from solution ..." Each of Claims 33, 49, and 50 has been amended to delete the phrase "from solution" and to clarify that the peptide is covalently linked to a water soluble, nonpeptidic polymer in a reaction mixture in which said peptide and said nonpeptidic polymer are present as reagents. Each of Examples 2, 4, 5, and 6 show that the reagents are reacted in a solution for conjugation of peptide to polymer. This clarifying amendment should obviate the rejections of Claims 33, 49, and 50 on the basis of the use of the phrase "from solution."

**C. Rejections of Claims 35 and Claim 36.**

Claims 35 and 36 have been rejected as unclear with respect to what in the peptide is being conjugated and for a typographical error. A period has been added at the end of Claim 36 to correct the typographical error. Claims 35 and 36 have also been amended to more succinctly state that the peptide is being conjugated at its terminus.

Thus, in view of the amendments and remarks presented above, it is submitted that the claims now comply with the requirements of 35 USC Section 112, second paragraph, and distinctly define the metes and bounds of the subject matter which the Applicant regards as the

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invention. Thus, it is submitted that the Examiner's rejections under 35 USC Section 112, second paragraph, have been overcome.

#### The Rejections Under 35 USC § 102

Claim 49 has been rejected under 35 USC § 102(b) as anticipated by Poduslo et al. U.S. Patent No. 5,670,477. The Poduslo reference discloses polyamine carrier compounds for neurologically active compounds. The carriers are said to be (i) peptides and (ii) polymers of the empirical formula  $C_xH_yN_z$ , said preferably to be peptides and proteins having high permeabilities to the blood nerve barrier or the blood brain barrier. See Column 15, lines 20 through 25 and Column 14, lines 63 through 66. Useful permeabilities are said to be at least 5 to 20 fold higher than that of the native neurologically active compound. The  $CH_2$  chains are said to be of 3 to 12 carbon atoms and the Poduslo carriers are of low molecular weight. No nonpeptidic hydrophilic polymers are disclosed or suggested.

In sharp contrast to Poduslo, none of the polyethylene glycol and related water soluble, non-peptidic polymers recited in Claim 49 have the empirical formula disclosed by Poduslo. Nowhere does Poduslo disclose the polymers recited by Applicant. Accordingly, the Poduslo reference does not anticipate Claim 49. Claim 49 is fully supported by the specification at pages 10 through 12.

#### The Rejections Based on 35 USC § 103

##### A. Rejections Based on Poduslo, Hruby, and Rodbard.

Claims 30 through 36, 45 and 50 have been rejected as unpatentable over the Poduslo reference considered in combination with Hruby et al. U.S. Patent No. 4,518,711 and Rodbard et al. U.S. Patent No. 4,468,383.

Poduslo is directed to carrier molecules covalently linked to neurologically active agents to improve the ability of the active agents to penetrate the blood brain barrier. The carrier molecules of Poduslo include (i) peptides and proteins with high permeabilities to the blood brain barrier, 5 to 20 times greater than the native neurologically active compound, which clearly fall outside of the non-peptidic polymers of Applicant's invention, and (ii) small polyamines having an empirical formula  $C_xH_yN_z$ . In Applicants' invention, it is the analgesic peptide that serves as a carrier, the nonpeptidic polymer serving to increase solubility and stability and to

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reduce immunogenicity of the analgesic peptide. See Applicants' specification at page 7 through 13. Nowhere does Poduslo teach or suggest polymers of the type recited by the Applicant.

Thus, Poduslo is directed to an entirely different structural class of molecules for modifying neurologically active compounds. Moreover, Applicants' conjugates have significantly different pharmacological properties from those of Poduslo. Poduslo's compounds demonstrate dramatically reduced half-lives in comparison to the corresponding native or unmodified proteins (Column 19, line 66 through Column 20, line 1). In contrast, the exemplary polyethylene glycol-modified proteins of Applicants' invention demonstrate significantly prolonged half-lives when compare to the corresponding native protein (Example 3).

The Hruby reference is directed to cyclic, conformationally constrained analogs of enkephalins that bind to delta receptors. No conjugation to nonpeptidic polymers is disclosed or suggested and administration is said at column 15, lines 25 through 45 to be by intracerebral injection, which is injection directly to the brain, not through the general circulation or by crossing the blood brain barrier.

The Rodbard reference is directed to enkephalin polypeptide monomers that are linked at the C-termini with a difunctional amino bridging group. No conjugation of these enkephalins to nonpeptidic polymers, including poly(ethylene glycol), is disclosed or suggested.

As set forth above, the Poduslo reference is directed to the conjugation of analgesic peptides with polyamines and not with poly(ethylene glycols) or the other related polymers disclosed to be useful in connection with Applicants' invention. Accordingly, even considered in combination, there is no disclosure or suggestion of the conjugate as set forth in Applicants' claims.

**B. Rejections Based on Poduslo, Hruby, Rodbard, and Harris.**

Claims 37 through 40 and 42 through 44 have been rejected as unpatentable over the Poduslo reference, the Hruby reference, the Rodbard reference and Harris et al. U.S. Patent No. 5,932,462, considered in combination. The Harris reference discloses that thousands of proteins and enzymes can be usefully modified by attachment to a branched poly(ethylene glycol) at column 36, line 27 through column 37, line 6. However, there is no disclosure or suggestion that any conjugate of a branched poly(ethylene glycol) or any other related polymer with an analgesic

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peptide can cross the blood brain barrier. Accordingly, there is no disclosure or suggestion or recognition in these references separately or in combination of the conjugates that are recited in Applicants' claims or of the ability of these conjugates to cross the blood brain barrier of a mammal.

Thus, none of the references, considered singly or in combination, suggest the invention as recited in Applicant's claims. Moreover, there is no motivation provided in either the references or based on common knowledge in the art at the time the invention was made to modify the teachings of the cited references to arrive at the claimed invention. Nothing in Poduslo or in any of the cited references leads one of ordinary skill in the art to modify the small polyamines of Poduslo to arrive at Applicant's polymers. Poduslo teaches away from the conjugates of the invention since Poduslo's conjugates have decreased circulating half-lives in comparison to the corresponding native proteins while the Applicants' conjugates tend to have circulating half-lives that are considerably increased over those of the unmodified protein.

Nor are the deficiencies of Poduslo made up by the secondary references. Motivation to combine references must come from the references themselves and not from hindsight based on Applicants' disclosure. One of ordinary skill in the art being apprised of the Harris reference would not be led to any suggestion that conjugates of the polymers recited by Applicant with an analgesic peptide could cross the blood brain barrier.

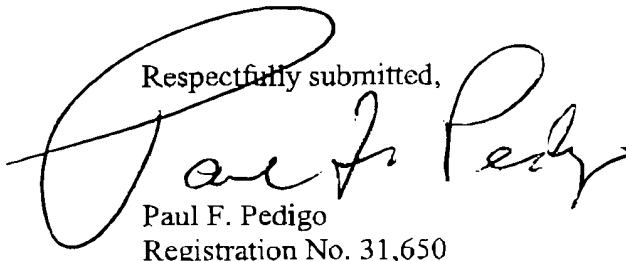
In sum, since none of the references teach or even remotely suggest a neuropeptide covalently bound to a polymer of the type recited in Applicants' claims to form a neuropeptide transportable across the blood brain barrier, then the invention cannot be considered obvious in view thereof.

The rejections of record having been addressed in full in the foregoing, Applicants respectfully submit that all of the pending Claims 30 through 56 are now in condition for allowance, and an early indication of the allowability of these claims is respectfully solicited. If the Examiner has any questions regarding the foregoing, it is respectfully requested that she contact the undersigned at (704) 444-1021 at her convenience to expedite allowance of this matter.

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It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



Paul F. Pedigo  
Registration No. 31,650

CUSTOMER NO. 00826  
ALSTON & BIRD LLP  
Bank of America Plaza  
101 South Tryon Street, Suite 4000  
Charlotte, NC 28280-4000  
Tel Charlotte Office (704) 444-1000  
Fax Charlotte Office (704) 444-1111  
CLT01/4549435v1

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**Version with Markings to Show Changes Made:**

30. (Amended) A substantially hydrophilic conjugate comprising an analgesic peptide that is either biphalin or [D-Pen2, D-Pen5] enkephalin (DPDPE) covalently linked to a water soluble, nonpeptidic polymer selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), [and] wherein said conjugate, when administered into the blood circulation of a mammal, can transport across the blood-brain barrier [of a mammal and said analgesic peptide is selected from the group consisting of biphalin and [D-Pen2, D-Pen5] enkephalin (DPDPE)].

31. (Amended) The conjugate of Claim 30, which when administered in the blood circulation of a mammal, has an [having the property of] extended duration of analgesic effect [in mammals] as compared to the native peptide.

33. (Amended) The conjugate of Claim 30 further characterized in that said nonpeptidic polymer and said peptide are conjugated in a reaction mixture in which the polymer and peptide are present as reagents [from solution].

35. (Amended) The conjugate of Claim 30, wherein said peptide is covalently linked to at least one terminus of said polymer [further characterized by conjugation of the peptide at least one terminus thereof].

36. (Amended) The conjugate of Claim 30, wherein said peptide is covalently linked at one of its N-termini to said polymer, [further characterized by conjugation of the peptide at least one N-terminus thereof]

45. (Amended) A pharmaceutical composition comprising a conjugate according to Claim 30 and a pharmaceutically acceptable carrier [for said conjugate].

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49. (Amended) A substantially hydrophilic conjugate comprising an analgesic peptide covalently linked [from solution] to a water soluble, nonpeptidic polymer in a reaction mixture in which said peptide and said nonpeptidic polymer are present as reagents, and wherein said polymer is selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), [and wherein] said conjugate is characterized by the absence of noncovalent bonds and can transport across the blood-brain barrier of a mammal, [and] said nonpeptidic polymer is characterized by the absence of lipophilic moieties, and wherein said peptide is selected from the group consisting of dynorphin A, enkephalins, double enkephalins, and endorphins.

50. (Amended) A substantially hydrophilic conjugate comprising an analgesic peptide that is either biphalin [D-Pen2, D-Pen5] or enkephalin (DPDPE) covalently linked [from solution] to a water soluble, nonpeptidic polymer in a reaction mixture in which said peptide and said nonpeptidic polymer are present as reagents, and wherein said polymer is selected from the group consisting of poly(ethylene glycol), copolymers of ethylene glycol and propylene glycol, poly(vinyl alcohol), poly(alkylene oxides), poly(oxyethylated polyols), poly(olefinic alcohols), poly(acryloyl morpholine), poly(vinyl pyrrolidone), poly(oxazoline), dextran, poly(hydroxyethyl methacrylate), [and wherein] said conjugate is characterized by the absence of noncovalent bonds and, when administered into the blood circulation of a mammal, can transport across the blood-brain barrier of a mammal, [and] wherein said nonpeptidic polymer is [characterized by the absence of] absent lipophilic moieties[, and wherein said peptide is selected from the group consisting of biphalin and [D-Pen2, D-Pen5] enkephalin (DPDPE)].